WHEN KIDNEY STONES MAY BE A SIGN OF SOMETHING MORE SERIOUS[1,2]

Primary hyperoxaluria type 1 (PH1):
A metabolic stone disease with potentially devastating consequences.[2-4]

Alnylam® PHARMACEUTICALS

Any unusual presentation among stone formers merits further investigation[1]

CHILD OR ADOLESCENT

- Any stone[1,5]
- Family history of stones[1]

ADULT

- Recurring stones[1]
- Multiple or bilateral stones[1]
- Stones that may be larger on average, such as staghorn stones[1,6-9]
- Family history of stones[1]
- Stones with unusual biochemical composition[1]

When patients present with kidney stones, a metabolic stone disease may be the cause[1,2]

34% of pediatric stones may be linked to a metabolic condition*,[10]

11% of adults presenting with kidney stones or nephrocalcinosis may have a causative mutation†,[11]

*Based on data from a retrospective review of 511 children at a single center.[10]
†Based on data from a cohort of 166 adult patients seen at tertiary centers.[11]

EXAMPLES OF METABOLIC STONE DISEASES[1,12,13]

- Primary hyperoxaluria type 1 (PH1)
- Primary hyperoxaluria type 2 (PH2)
- Primary hyperoxaluria type 3 (PH3)
- Cystinuria
- Absorptive hypercalciuria
- Xanthinuria
- Dent disease
- Renal hypouricemia
- Renal hypomagnesemia
- Distal renal tubular acidosis

The American Urological Association (AUA) recommends metabolic testing through 24-hour urine collection analysis in high-risk and interested first-time stone formers for substances including oxalate and stone-forming salts.[14]

BEHIND THE STONE™

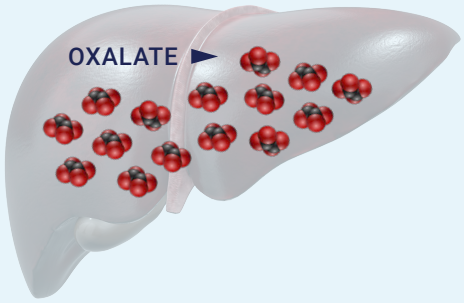
PH1 is a progressive, life-threatening, inherited disease that often presents with kidney stones[2-4]

PH1 is caused by autosomal recessive mutations in the *AGXT* gene.[3,4]

PH1 is rare and remains underdiagnosed in clinical practice.[8,15-18]

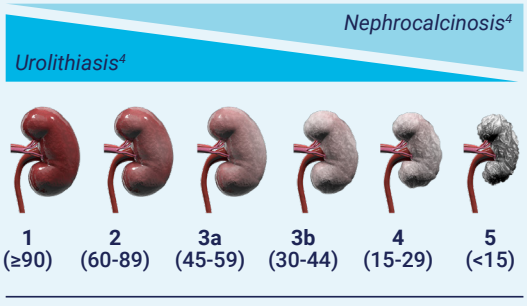
PH1: A METABOLIC DEFECT IN THE LIVER[3,4,19]

- *AGXT* gene mutations impair the function of a liver enzyme called AGT[4,19]
- Oxalate, a toxic metabolite, is continuously overproduced as a result[3,4]



EXCESS OXALATE DAMAGES THE KIDNEYS[2,4]

- Oxalate is primarily renally excreted[4]
- Oxalate forms calcium oxalate crystals that can aggregate to form kidney stones or deposit into kidney tissue and lead to nephrocalcinosis[3,8]
- Over time, oxalate overproduction can lead to progressive kidney function decline[2,4]



Chronic kidney disease (CKD) stages[20]
(Estimated glomerular filtration rate [eGFR] range [mL/min/1.73m²])

BEHIND THE STONE

PH1 can present in children and adults[3]

PH1 patients with identical genotypes, and even members of the same family, can have variable disease presentations.[2]

SIGNS OF PH1 TO LOOK FOR

Kidney stones are the most common clinical manifestation and the one that most often leads to a diagnosis of PH1, though not all patients with PH1 may be stone formers.[8,21,22]

CHILDREN/ADOLESCENTS	ADULTS	ALL AGES
Any stone[1,3,4]	**Unusual* and/or recurrent stones**[1,2]	**Family history of stones**[1]

*Including multiple, bilateral, and/or large stones.[1,2]

Other possible signs

Failure to thrive in infancy[3]

Nephrocalcinosis[2-4,8]

Progressive kidney function decline[2,4]

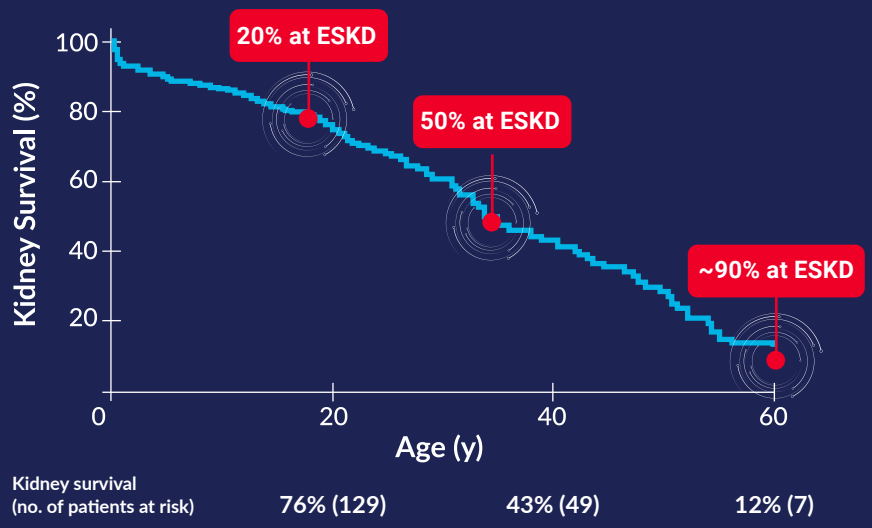
BEHIND THE STONE

Continuous oxalate overproduction causes progressive damage in the kidneys and other organs[8]

PH1 can lead to a progressive decline in kidney function with eventual advancement towards end-stage kidney disease (ESKD), though the rate is variable.[3,8,18,23,24]

- Patients with higher urinary oxalate (UOx) excretion progress more quickly to ESKD[25]
- In some instances, kidney function can decline after a single incident of dehydration due to acute illness or intense physical activity[9,26,27]
  - This can occur even in patients with previously stable kidney function[26]

PATIENTS TYPICALLY PROGRESS TO ESKD*,[18]



*Based on retrospective kidney survival data from 247 patients with PH1 from the Rare Kidney Stone Consortium Registry.[18]

Figure adapted from Hopp K, et al. J Am Soc Nephrol. 2015;26:2559–2570.

As kidney function declines, the kidneys are unable to excrete oxalate effectively and systemic oxalosis can occur.[8,28]

Oxalate spreads and forms crystals throughout the body—including in the bones, joints, retina, and heart.[8,28]

BEHIND THE STONE

Given the progressive, unpredictable nature of PH1, early diagnosis is critical[3,8]

If PH1 is suspected, common methods seen in clinical practice to test for the disease include (but are not limited to):

MEASURING OXALATE LEVELS

In patients with **preserved kidney function:**

24-HOUR URINE TEST[14,19,29]

Normal UOx level (all ages):
<0.50 mmol (<45 mg)/1.73 m^2/24 hours[2]

Spot testing can be used when 24-hour urine test is not possible.[8]

In PH1, UOx levels are often between 2 to 5 times higher than the upper limit of normal.[30]

In patients with **impaired kidney function**:

PLASMA OXALATE MEASUREMENT[8,19,31]

Normal plasma oxalate level: ≤2 µmol/L*[,32]

Substantially elevated levels are typical when eGFR <30 mL/min/1.73 m^2. Levels >50 µmol/L are suggestive of PH1.[3]

GENETIC TESTING

Identifying *AGXT* gene mutations with genetic testing can help confirm a PH1 diagnosis with high sensitivity and specificity.[19,33]

It is recommended to screen family members of a patient with PH1, especially siblings.[8,19]

The AUA recommends genetic testing to confirm a PH1 diagnosis in any patient with UOx excretion exceeding 0.83 mmol/1.73 m^2/day (75 mg/day).†,[14]

*Reference values have not been established for patients under 18 years old or greater than 87 years of age.[32]
†In adults without bowel dysfunction.[14]

5.5 years

is the median delay in adults between onset of clinical manifestations and diagnosis.[16]

Historically, PH1 has a low index of suspicion due to:

- Its rarity[15]
- Nonspecific nature and lack of follow-up on kidney stone events[8,17]
- The fact that nephrocalcinosis and declining kidney function may occur without symptoms[8]

BEHIND THE STONE

Alnylam Act® is one option for genetic testing and counseling

The Alnylam Act® program was created to provide access to genetic testing and counseling to patients as a way to help people make more informed decisions about their health.

- While Alnylam provides financial support for this program, tests and services are performed by independent third parties
- Healthcare professionals must confirm that patients meet certain criteria to use the program
- Alnylam receives de-identified patient data from this program, but at no time does Alnylam receive patient-identifiable information. Alnylam uses healthcare professional contact information for research and commercial purposes
- Genetic testing is available in the US and certain other countries. Genetic counseling is available in the US
- Healthcare professionals or patients who use this program have no obligation to recommend, purchase, order, prescribe, promote, administer, use, or support any Alnylam product
- No patients, healthcare professionals, or payers, including government payers, are billed for this program

For more information about these third-party programs, visit AlnylamAct.com.

KNOW THE SIGNS AND IDENTIFY PH1 EARLIER

PH1 is a progressive, life-threatening, inherited disease that often presents with **kidney stones.**[2-4]

Oxalate overproduction from the liver **primarily damages the kidneys,** with eventual advancement toward ESKD.[2-4]

PH1 remains underdiagnosed. **Metabolic testing** can raise suspicion of PH1 and **genetic testing** can help confirm a diagnosis.[8,14-17]

Alnylam Act® is one option for genetic testing.

For more information, visit AboutPH1.com

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